Analysis of Mediating Variables

"How do our interventions work?"

Mediation

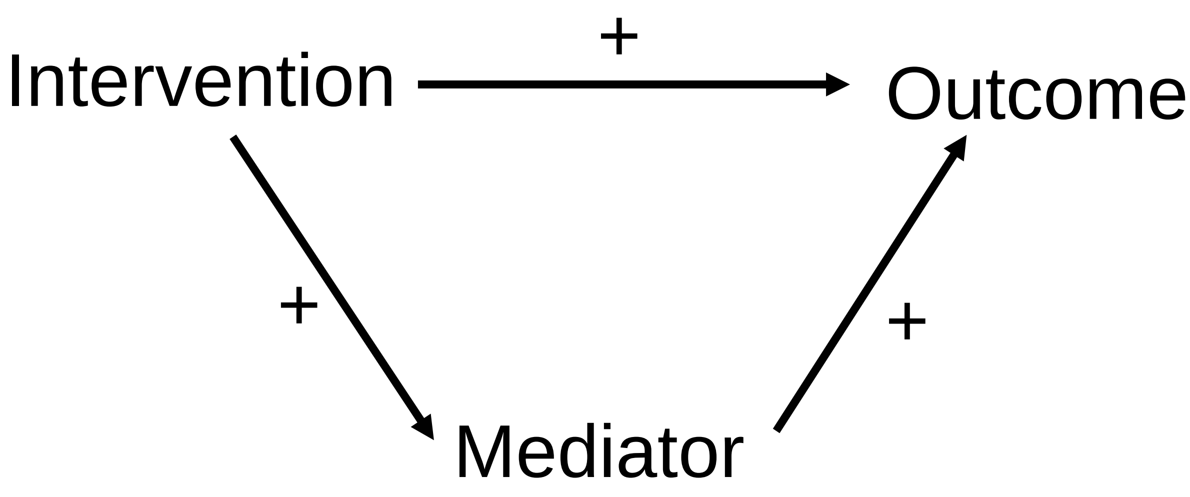
- Suppose an independent variable (*X*) is shown to have an effect on a dependent variable (*Y*).

Intervention $\xrightarrow{+}$ Outcome

- Often want to explore a third variable to elucidate the causal process by which *X* affects *Y*.

Mediation

- Mediators identify potential mechanisms through which a treatment works (why and how treatment has an effect)



- Mediators are variables that underlie the relationship between *X* and *Y*. It is affected by *X* and affects Y.

Can third variable be a confounder?

- Yes. But, in the setting of RCT, randomization should remove confounding effects.

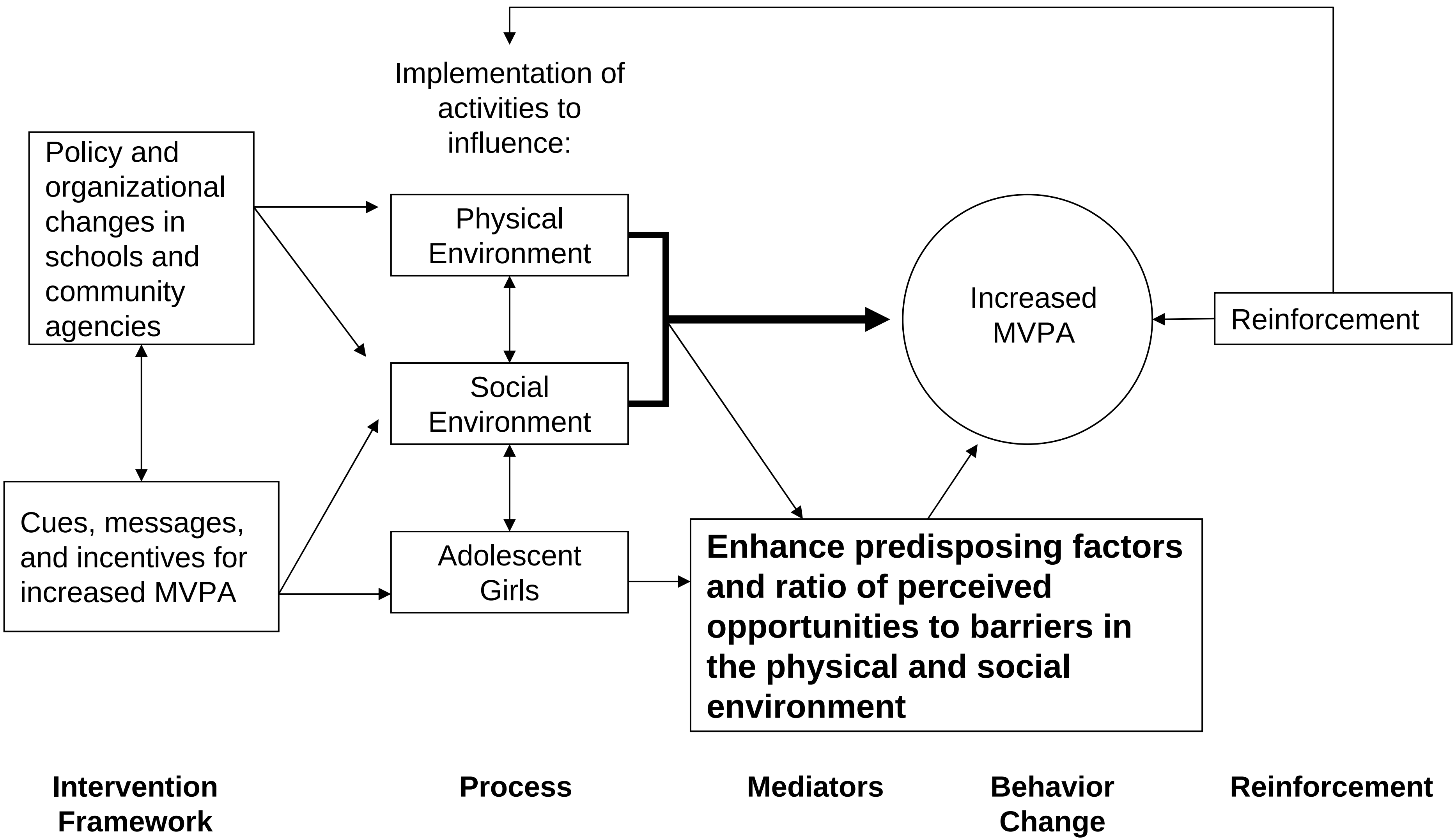
- Confounders are often demographic variables (age, gender, race) that typically cannot be changed in a RCT

- Mediators are by definition capable of being changed.

Mediating variable framework

- Behavioral interventions are typically based on theories of behavior change ("theoretical model"), whereby intervention components are selected based on their ability to change the outcome of interest

TAAG Social-Ecological Model



TAAG intervention components

- Promotions
  - Inform school staff, students, community agencies about physical activity opportunities (announcements, posters, flyers)
  - Reinforcement and incentives (pedometer challenge, Passport program)
  - Foster <u>positive</u> family, peer, and school social norms around being an active girl

TAAG intervention components

- Health Education with Activity Challenges (HEAC)
  - Focuses on skill development, increasing awareness of opportunities to be active and promoting enjoyment of being active

  - Challenges target goal-setting and reinforcement of behavior change

Sample HEAC lesson

- Barrier Busters! Identifying and Breaking Barriers to Physical Activity

  – Brainstorm ways to break through common barriers to being active in small groups

  – Challenge: Jump the Barrier
    - Jump rope challenge for the week: 500 jumps/day for a week

TAAG intervention components

- TAAG PE
  - Provide a PE experience where girls enjoy participating in class activities and increase their competence in being active
  - Engage girls in MVPA for at least 50% of class time

TAAG intervention components

- Partners for Physical Activity
  - School-Community partners that increase availability and accessibility of girl-friendly out-of-school activity programs

Potential Mediators

- Self-efficacy
  - confidence in overcoming barriers
- Change strategies
  - cognitive and behavioral strategies to adopt and maintain regular physical activity
- Enjoyment of PA
- Enjoyment of PE
- Perceived benefits, barriers

Potential Mediators

- Social support
  - Assist, reinforcement participation in physical activity especially when individual perceives disadvantages or deficit in resources needed to be active
- Perceived environment
  - girl-friendly activities in community agencies,
  - exposure to new settings could change knowledge of, and perceptions about, recreational facilities
- School climate for PA

Mediating variable framework

- Mediation analysis can help identify the critical components of interventions, but only if mediating variables can be <u>quantified</u> adequately and are <u>measured</u>!

- If interventions are found to have an effect that is not explained by mediating variables, the theory may need further development

Mediating variable framework

- Identification of strong mediators through which the intervention operates can help guide development of interventions in the next generation of studies

- Effective components can be intensified and refined, and ineffective or redundant components discarded.

Statistical methods for assessing mediation

- Baron RM, Kenny DA. The moderator-mediator variable distinction is social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol* 1986;51:1173-1182.

- Kraemer HC *et al*. Mediators and moderators of treatment effects in randomized clinical trials. *Arch Gen Psychiatry* 2002;59:877-883.

Statistical methods for assessing mediation

- To show that *M* is a mediator of the intervention effect
  a) *M* has to measure an event or change occurring during treatment (baseline measure cannot be a mediator)
  b) Intervention is significant predictor of outcome
  c) *M* is correlated with the intervention, hence is possibly a result of the intervention
  d) *M* has a main or interactive effect with the intervention on the outcome

Notes

- A post-treatment measure that is correlated with treatment, which has neither a main nor an interactive effect on outcome, is an independent outcome of treatment

- Example: A CVD risk reduction program (intervention) increases activity level (outcome) and reduces weight, but the decrease in weight is not correlated with increased activity level
  - Weight reduction and activity increase are 2 independent outcomes.

Notes

- Measures related to treatment implementation should not usually considered as mediators
- Example: If intervention is pharmacologic or psychotherapy, we are not interested in blood level of the medication or attendance at therapy sessions as possible mediators
- Exception: in multi-component intervention, could be used to show how strongly each component mediated the treatment response

Notes

- Baron and Kenny (1986) proposed that a variable is a mediator if it directly influences the outcome (main effect only).

- Kraemer (2002) points out that mediation also occurs if the intervention causes a change in the variable and in the impact of the variable on the outcome (interactive effect)

Statistical methods for assessing mediation

- A variable is a mediator if statistical adjustment for the variable <u>reduces</u> the magnitude of the intervention effect on the outcome

  $\Rightarrow$ mediator explains part of the intervention-response relationship.

- The strength of the mediating effect may be estimated by the proportion of intervention effect that is explained by the mediating variable

Statistical methods for assessing mediation

- A natural estimate is $1 – (\tau_{adj} / \tau)$
  - τ_{adj} is the adjusted intervention effect estimate, τ is the unadjusted estimate
  - To calculate confidence limits for $1 – (\tau_{adj} / \tau)$ see Freedman *et al*. (1992)

- Could also use $(\tau_{adj} - \tau)$
  - 95% CI: $(\tau_{adj} - \tau) \pm$ s.e.$(\tau_{adj} - \tau)$

  where $\text{var}(\tau_{adj} - \tau) = \text{var}(\tau_{adj}) + \text{var}(\tau) - 2\text{cov}(\tau_{adj},\tau)$

Example: LRC-CPPT

- Lipid Research Clinics Coronary Primary Prevention Trial
  - RCT to test the efficacy of cholesterol lowering drug for reducing CHD
  - Average follow-up of 7.4 years
  - Incidence of CHD was 19% lower in treated group
  - To what extent was the treatment effect mediated by change in total cholesterol?

Example: LRC-CPPT

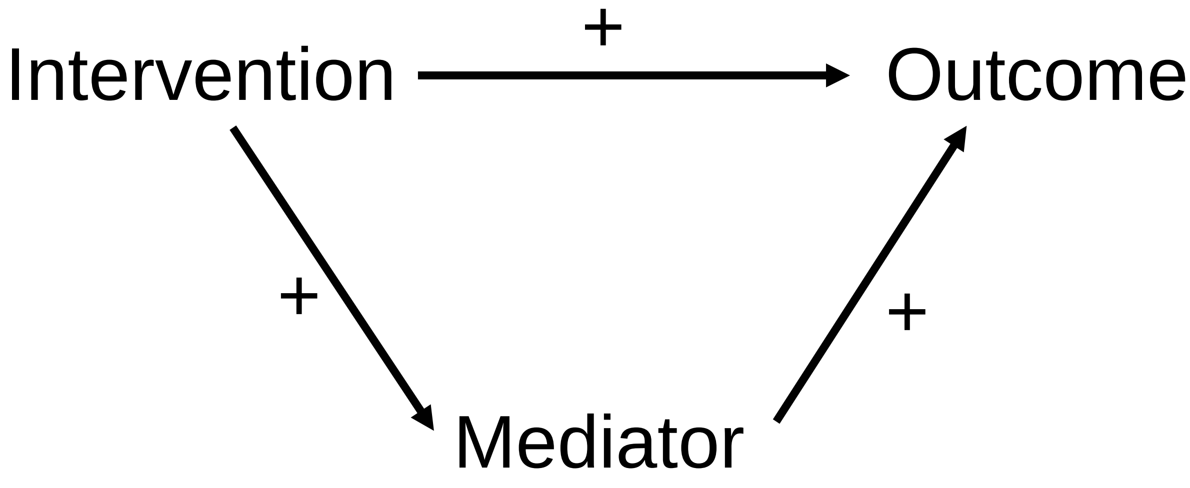
- Mediator: cholesterol level at 1 year
- Only CHD events occurring after 1 year are included
- For simplicity, assume each subject has same length of follow-up and treat the outcome as binary (event/no event)

Example: LRC-CPPT

Cholesterol (mg/dl) at year 1	Event Rate (events/patients at risk)x100	
	Placebo	Cholestyramine
< 180	0	8.5
180-230	8.8	5.0
230-280	7.3	7.3
280-330	10.1	7.6
> 330	15.7	16.4

Example: LRC-CPPT

- Treatment reduces CHD events
- Treatment reduces cholesterol level
- Cholesterol level is related to CHD risk



Example: LRC-CPPT

Model:	Estimated treatment effect	SE	P
$\ln(p/(1-p)) = \mu + \tau$	-.26	.12	.03
$\ln(p/(1-p)) = \mu + \tau + \lambda$	-.13	.13	.30

- Change in cholesterol levels explains half
  1- (-.13/-.26) of the observed treatment effect

Example: LRC-CPPT

- The change in the coefficient for the treatment effect is 0.13.

  $\mathrm{var}(\tau_{adj} - \tau) = .12 + .13 - 2(.015) = .00324$

  $\mathrm{s.e.}(\tau_{adj} - \tau) = .0569$

- 0.13 (95% CI: 0.02 - 0.24; p=0.024)

Example: LRC-CPPT

- 1-year cholesterol level doesn’t represent the change over 7.4 years of follow-up

- Measurement error in your mediator will bias the treatment effect adjustment

  – Can take measurement error into account (e.g., Carroll *et al*. 1984)
  – Use structural equation modeling
  – Use composite measures for constructs with multiple measures

Example: LRC-CPPT

- Can also take a “meta-analysis” perspective if many RCTs have measured both mediator and outcome

- Correlate observed change in mediator with observed treatment effect on the outcome

Discussion

- Mediator analyses are hypothesis-generating rather than hypothesis-testing.
- In evaluation of RCTs, there is a tendency to dismiss such analyses as “data dredging”
- But such analyses are critical in identifying strong mediators that should be considered when constructing interventions to be evaluated in the next RCT.

Discussion

- Although mediator analysis is post-hoc, the decision to perform such an analysis must be a priori.
- Want to select measures which theory or experience suggest as possible mediators without overburdening the subjects.
- Need to think carefully about how often to measure the mediator

Discussion

- There is some evidence of a rapid response to CBT for treatment of disorders.
  - 60-70% of total improvement in depression occurs in first 4 weeks of CBT (Ilardi, Craighead 1994)

- Potential mediators are often measured after much of the therapy effect has already occurred.

- With such a rapid initial response, mediators have to be measure early, perhaps on a session-by-session basis.